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Effect of Segmental Bronchoalveolar Lavage on Quantitative Computed Tomography of the Lung

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Abstract

Rationale and Objectives—With employment of both multi-detector computed tomography (MDCT) and endobronchial procedures in multi-center studies, effects of timing of endobronchial procedures on quantitative imaging (Q-MDCT) metrics is a question of increasing importance.

Materials and Methods—Six subjects were studied via MDCT at baseline, immediately following and at 4hrs and 24hrs post-BAL (right middle lobe (RML) and lingula). Through quantitative image analysis, non-air, or 'tissue' volume (TV) in each lung and lobe was recorded. Change in TV from baseline was used to infer retention and re-distribution of lavage fluid.

Results—Bronchoscopist reported unrecovered BAL volume correlated well with Q-MDCT for whole lung measures, but less well with individual lobes indicating redistribution. TV in all lobes except the RLL differed significantly ($p<.05$) from baseline immediately post lavage. At 24hrs, all lobes except the LLL (small 1% mean difference at 24hrs.) returned to baseline.

Conclusions—These findings suggest fluid movement, effecting Q-MDCT metrics, between lobes and between lungs before eventual resolution, and preclude protocols involving the lavage of one lung and imaging of the other to avoid interactions. We demonstrate that Q-MDCT is sensitive to lavage fluid retention and re-distribution, and endobronchial procedures should not precede Q-MDCT imaging by less than 24hrs.

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Institution: All work was performed at The University of Iowa Hospitals and Clinics, Iowa City, IA.

Conflict of Interest Disclosure: Mr. Gabe has no conflicts of interest to disclose. Dr. Baker has no conflicts of interest to disclose. Dr. van Beek is founder and president of Quantitative Clinical Trials Imaging Services, Inc., which is a service provider to imaging-based clinical trials (both commercial and academic). Dr. Hunninghake has no conflicts of interest to disclose. Dr. Reinhardt is a shareholder in VIDA Diagnostics Inc. that is commercializing image analysis software used in this study. Dr. Hoffman is a founder and shareholder of VIDA Diagnostics Inc. that is commercializing image analysis software used in this study. The University of Iowa receives royalties from VIDA Diagnostics, Inc.

Keywords

Bronchoscopy; Lavage; Lung Fluid; Multi-center trials; Quantitative Computed Tomography

INTRODUCTION

This study seeks to understand the interaction of bronchoalveolar lavage (BAL) and quantitative measures obtained from multidetector-row X-ray computed tomography (Q-MDCT). There has been considerable effort to utilize regional lung density measures from Q-MDCT for the objective assessment of lung pathology (1–4) Q-MDCT density measures have been shown to accurately reflect regional air and non-air content of the lung (5), and comparisons with biopsy samples have been made in humans to validate these measures (6).

BAL is used in pulmonary research and clinical practice as a means of access to the lung parenchyma. During the lavage procedure, 30–40% of instilled saline is left unrecovered in the lungs of healthy patients. The unrecovered volume is increased in smokers and patients with obstructive lung disease (7–9]). Volumes of individual aliquots instilled by both clinicians and researchers vary, usually between 20–200ml; approximately 100–200ml cumulative saline is used at each site(10). Despite BAL's wide use as an academic, diagnostic, and therapeutic tool, specifics of the procedure are not standardized and many results are susceptible to a great degree of uncertainty, as summarized by Baughman(11, 12). Of particular importance in recent efforts to establish study designs for complex multi-center studies of the lung has been the question of how to sequence an endobronchial procedure relative to a Q-MDCT study. With the difficulty of scheduling the Q-MDCT exam and the pressure to complete a series of procedures in a single day, there have been efforts to simply allow the Q-MDCT scan to float within the order of procedures. Little is known, however, of the fate or consequences of unretrieved saline. Klein et al. (13) have demonstrated that for as much as an hour or longer post BAL, lung mechanics as well as blood gases can be significantly altered. This is of interest as one might not expect that a localized alteration of a single lobar segment would change lung mechanics. Imaging studies of BAL fluid itself are largely limited to chest films and V/Q scans (14, 15). One such study found a correlation between volume of retained fluid and qualitative measures of opacity on immediate post-lavage images; these opacities cleared after 24 hours (15). Though studies have combined both Q-MDCT and BAL as adjuncts in patient treatment or even compared their respective diagnostic values (16–19). CT data of BAL fluid itself is minimal. The effects of BAL on Q-MDCT is critical, particularly when Q-MDCT measures are being sought to follow, for instance, progression of emphysema when it has been shown that such changes are on the order of 2.5 Hounsfield Unit change in lung density per year (1, 2, 6).

In the present study, we have utilized image data from another IRB approved research study to pursue two goals: 1) to evaluate subjects before and after a bronchoalveolar lavage (BAL), so as to take advantage of known volumes of lavage left behind as an index against which we can assess the presence and subsequent resolution of fluid volumes by Q-MDCT assessment of the "non-air" volume within the lung; and 2) to evaluate the distribution and clearance of unrecovered BAL fluid over a 24 hour period post lavage to better understand how Q-MDCT metrics are affected in un-targeted regions of the lung.

MATERIALS AND METHODS

Subjects

The protocols for CT imaging as well as our use of the image data was reviewed and approved by the University of Iowa Institutional Review Board. All participants signed

informed consent before the study. Subjects were anonymized, and the study was conducted in compliance with HIPAA requirements. Six healthy non-smokers agreed to participate and had no recorded exclusion criteria (recent respiratory infection, medication other than contraception, cardiopulmonary abnormalities, pregnancy or breast feeding, diabetes mellitus, positive PPD or history of tuberculosis, CT scan within the last year). Screening was done by interview, questionnaire, and baseline pulmonary function test (PFT).

Study Design

Timeline—The study involved Q-MDCT scans of each subject at four time points: baseline, immediate post-lavage, four hours post-lavage, and 24 hours post-lavage. Subjects were NPO after midnight prior to the procedure. Upon reporting, vital signs, height, and weight were obtained, consent was reviewed, and subjects underwent PFT. Pregnancy tests were conducted for women of child-bearing age. Premedications for bronchoscopy were initiated according to standard protocol (Atropine 0.6 mg IM; Morphine 10 mg IM or Meperidine 25 mg IM with Promethazine 12.5 mg IM), after which baseline CT scans were obtained in the Iowa Comprehensive Lung Imaging Center's (I-Clic) research CT suite.

Subjects were transferred to the clinical bronchoscopy lab, where BAL was performed distal to a wedged bronchoscope in a subsegment of the right middle lobe and lingula with sterile saline warmed to 37 degrees Celsius. Each subject received aliquots of 5 × 20 (100) ml in one lung and 4 × 50 (200) ml in the contralateral lung; assignment of which side received which aliquots alternated between subjects. Lidocaine was applied topically as an anesthetic. BAL fluid was retrieved from each site and measured by the bronchoscopist. The volumes delivered and retrieved coupled with a calculation of volume unretrieved is tabulated in Table 2. As shown in Table 2, Subject 2 was observed to cough a significant amount of BAL fluid out of the lungs.

Subjects were transferred back to the I-Clic research CT suite via a wheel chair (approximately 3 minutes from bronchoscopy suite), where they underwent the post-lavage scan within 30 minutes of lavage. After scanning they were transferred to the University of Iowa Clinical Research Unit (CRU) for recovery. Vital signs were measured every 15 minutes by a nurse for two hours, and subjects were allowed to eat and drink after return of their gag reflex. Another scan was performed in I-Clic at four hours post-lavage, after which subjects were allowed to spend the night in the CRU or return home if someone was available to drive them. Subjects returned the next day for the 24 hour post-lavage scan.

CT Imaging—All scans were performed using the same scanner protocol (120 kVp, 80 mA, 40 effective mAs), and the same scanner (Siemens Sensation Cardiac 64, Siemens Medical Solutions: Forchheim, Germany). Initial slices obtained for all scans were 0.75 mm; these were reconstructed to 0.5 mm slice intervals. Scans were reconstructed using a B31f reconstruction kernel.

Analysis—Images were evaluated by an experienced Chest Radiologist(EvB) who reported on the overall appearance, in particular the presence and location of ground glass changes. Further evaluation of reconstructed scans was conducted by use of the Pulmonary Workstation 2 image analysis software package. (PW2: VIDA Diagnostics, Coralville, Iowa, USA). Airways (20), vessels (21) lungs (22) and lobes (23) were segmented. Air, non-air, and total volume (5) were recorded from each lung and lobe. All quantitative image analysis was performed by one person after completion of all subject scans.

Estimation of retained Bronchoalveolar Lavage saline—A traditional metric employed in volumetric CT is the density histogram. Picture elements (voxels) are counted

and arranged in a frequency distribution according to their grayscale intensity. Voxel intensity, measured in Hounsfield Units (HU), is linearly correlated with physical density. Assuming that the lung is a mixture of two materials: air (−1000 HU) and blood/tissue (+55 HU), the air and non-air fraction of each voxel can be calculated (5) Performing this measurement over all voxels in the lung or lung lobes, one can obtain a measure of total air and non-air volumes.

Parenchymal attenuation assessed by CT and measured by PW2 as ‘non-air’ or ‘tissue’ volume includes blood, extravascular fluid, and lung tissue. Lavage fluid cannot be parsed from the other components of non-air volume using a single scan, but we sought to estimate it by comparing post-lavage to pre-lavage scan data, using the following equation:

$$\text{Retained lavage fluid} = (TV_{\text{Time x}}) - (TV_{\text{Baseline}})$$

where $TV_{\text{Time x}}$ is the non-air volume within a segmented area of the CT scan at a time *x* after lavage, and TV_{Baseline} is non-air volume within that area before lavage. In the interest of standardization among patients, values are reported as a percentage of baseline non-air values, as shown in this expression:

$$\frac{(TV_{\text{Time x}}) - (TV_{\text{Baseline}})}{(TV_{\text{Baseline}})} \times 100\%$$

RESULTS

Subject Characteristics

As shown in Table 1 the subject pool was divided among males and females with an average age of 25 yr and a range of 20–37 yr. Mean percent predicted FEV_1 (%FEV_1), percent predicted FVC(%FVC), and FEV_1/FVC were 95.2, 96.2, and 83, respectively. Instillation and aspiration of lavage fluid was frequently followed by coughing. A small amount of fluid was occasionally expectorated (the exception was patient #2 described above who expectorated a large volume of fluid). Subject 1 developed a modest fever. No therapy was required and the fever resolved overnight. Prior to bronchoscopy, the patient denied any recent fevers or upper respiratory symptoms. Subsequently, the subject disclosed that he had actually had a recent upper respiratory tract infection approximately two weeks before the study.

Visual Assessment

Ground glass changes were observed in the right middle lobe and lingula in all subjects. In three subjects, there was some immediate overspill into the right lower lobe and in one subject both the right lower and right upper lobe showed changes at the immediate post BAL CT study. After 4 hours, ground glass changes were less prominent in the middle lobe and lingula, but developed in the right lower lobe in two subjects and in the right lower and upper lobes in one subject. In two of the subjects, complete clearance was observed at 24 hours, whereas some residual ground glass changes were seen in the right middle lobe (1 subject), lingula (1 subject), right lower lobe (1 subject) and right lower and upper lobe (1 subject).

Quantitative Assessment of Retained BAL Fluid

Figure 1 demonstrates the relationship between the amount of lavage fluid reported as retained by the bronchoscopist and the amount measured at the immediate post-lavage scan,

using the equation described above. The R^2 value describing this correlation when fluid in both lungs was summed together (Fig. 1 top) was .79. The slope of the linear regression line was .84 with an intercept of 4ml. When measuring the correlation between reported and assessed fluid by separate lung, R^2 values were .76 and .24; slopes of the linear regression lines were .56 and .21 and the intercepts were 17 and 33 ml for the left and right lungs, respectively.

The reported volumes of lavage fluid delivered to the left and right lobar segments are presented in Table 2. As noted, subject 2 expectorated a "large," though unmeasured, amount of fluid immediately following BAL. When this subject is removed from the relationships depicted in Figure 1, the results change significantly: the R^2 value describing both lungs summed together improves from 0.79 to 0.94, and the slope changes from 0.83 to 1.0. The R^2 of the left lung improves from 0.76 to .84 with the slope changing from 0.56 to 0.73, while the R^2 of the right lung worsens from 0.24 to 0.15 with the slope changing from 0.21 to 0.52. This suggests to us that the fluid coughed out came largely from the right lung.

In all subjects, except for subject 1, the lung receiving the greater volume of lavage fluid was verified to retain the greater volume of fluid as assessed from the immediate post lavage MDCT scan. However, in all subjects, other than subject 1, both lungs returned to baseline values at 24 hours regardless of which lung received the greater volume of lavage fluid. In Figure 3, we provide graphs of CT-derived retained fluid for each subject.

Figure 2 shows a sample coronal section over time with and without color-coded over-lays demarcating the lobar segmentation from one representative subject. The graphs show percent change in non-air volume relative to baseline for the left and right lungs and their individual lobes as a mean for all 6 subjects. Values plus or minus the standard deviations along with statistical significance ($P \leq 0.05$) are shown in Table 3. Regions with lavage fluid are visible within the right and left lungs (denoted by arrows). For the subject depicted in Figure 2, lavage fluid was delivered to the right middle lobe and to the lingula. Fluid accumulation is visible in the CT data immediately post lavage and at 4 hours in the right and left middle lobes, but in the left lobe, the fluid is present beyond the lingula. In all subjects, non-air volume increased significantly in the left upper lobe, left lower lobe, right upper lobe, and right middle lobe. Without quantitative assessment, this is not appreciated visually. These significant increases within non-lavaged lung regions, coupled with the fact that the whole lung fluid increase matches the bronchoscopist's report of unretrieved fluid while individual lung results do not, suggests that fluid re-distribution occurs not only amongst lobes on a single side of the lung but also between lungs. As shown both graphically in Figure 2 as well as statistically in Table 2, all lavage fluid was resorbed and non-air volumes returned to baseline within 24 hours except for the left lower lobe, which remained significantly different from baseline even at 24 hours. As seen in Figure 3, there was variability amongst subjects regarding how the unretrieved lavage fluid was re-distributed as might be expected, possibly depending upon such factors as coughing and body posture between scans, etc.

DISCUSSION

Validation of Approach

The eventual clearance over 24 hours of lavage-associated opacities described in a previous radiograph study (15) is similar to the Q-MDCT findings of this study. The current study demonstrates the significant effect that BAL has on Q-MDCT derived measures of regional lung density throughout the lung during the 24 hour period post BAL.

The relationship between reported unretrieved BAL fluid volume and Q-MDCT non-air volume changes immediately post-lavage is demonstrated in Figure 1 (top), which shows a positive correlation with a slope of 0.84 and R^2 of 0.79. The correlation is not 1.0 nor should it be: when the clinical observations of coughing and occasional expectoration following lavage are considered, CT-based assessment should underestimate that reported by the bronchoscopist. This is reflected by the slope of the linear regression in Fig. 1 (top), which is less than 1. The change in our results upon removing Subject 2, who expectorated an especially large amount of lavage fluid immediately post lavage, supports our conclusions as the R^2 value of both lungs measured together increases to 0.94, and the slope of the linear regression changes to 1.0.

Assessment of Unretrieved Fluid Behavior, Distribution, and Clearance

Given the good correlation of unretrieved fluid as reported by the bronchoscopist and as calculated by Q-MDCT when both lungs are measured in aggregate (Fig. 1 top), it is of interest that the correlation becomes strikingly worse when lungs are considered individually. Our protocol was to deliver a greater volume of fluid to one lung than to the other; however, R^2 values are worse in both individual lungs (Fig. 1 bottom panels). If fluid is re-distributed between lungs through change in body posture and coughing, it would be expected that the whole lung fluid gain would correlate better with the bronchoscopist's report than would either lung alone. These observations demonstrate the global nature of the lung density changes following a lavage procedure and the caution needed when interpreting lung density-derived values (including quantitative measures of emphysema or fibrosis) within 24 hours post bronchoscopic procedure.

It is also of interest that after significantly ($p<.05$) different non-air volumes (as a percentage of baseline) were measured in nearly all lungs and lobes at the immediate post-lavage scan, all measured lung regions return to an insignificant difference from baseline with the exception of the minor (1% on average) remaining deviation in the left lower lobe (Table 3). This finding quantitatively corroborates previous qualitative radiographic observation of BAL fluid, [15] and further suggests redistribution of fluid. The fluid appears to redistribute eventually to the dependent regions of the lung.

Fluid movement between lobes is further supported by the individualized data (Fig. 3). For example, in the left upper lobe of Subject 5 (Fig. 3.e), there was the expected initial increase in non-air volume immediately post-lavage; however, at the four-hour scan the expected decrease in left upper lobe non-air volume was paired with a concurrent increase in non-air volume in the left lower lobe. The concurrent increase was such that, in the four-hour scan, the left lower lobe demonstrated more non-air volume relative to its baseline value and showed a greater increase over baseline than was observed in the left upper lobe for this time point. This individualized data supports the same interlobar movement suggested by the aggregate data. Our finding that lavage fluid can be seen to effect the whole lung provides an explanation regarding how lavage of a single lobar segment[13] can be observed to effect total pulmonary mechanics for more than 3 hours post lavage.

Analysis of one BAL subject following a febrile response

The case of Subject 1 represents an interesting opportunity to assess post-lavage lung behavior as long as two weeks after a presumed viral respiratory infection. The results of this subject's Q-MDCT-based assessment of non-air volume as a percentage of baselines are especially notable at the four-hour scan. At this time point, Subject 1 had uniquely experienced an increase in his non-air lung volume above the amount recorded at the immediate post-lavage scan (Fig. 3.a). This increase in non-air volume relative to baseline occurred in both lungs; especially striking were the increases in the lower lobes.

In summary, in this study we have demonstrated the effectiveness of our method of pulmonary assessment to track the quantitative changes in lung density following a BAL. We have also sought to further elucidate the consequences of retained lavage fluid on regional Q-MDCT measures, and expand upon the limited body of radiographic knowledge directly concerning bronchoalveolar lavage. Our results are notable for the observation that lavage fluid movement amongst lobes, and even from lung to lung, in the 24 hours following lavage has significant effects on quantitative measures of regional lung density, and thus would be expected to significantly alter such measures as percent emphysema-like lung whereby voxels which fall below a fixed density threshold are counted.[1, 2, 6] We conclude that our method is effective in assessing the lungs and suggests a previously unmentioned propensity for retained BAL fluid to move amongst lungs and lobes before resolving after 24 hours, possibly explaining previously observed global alterations in lung mechanics from lavage of a single segment.[13] Retained fluid re-distribution was not visually noted and is only assessed by Q-MDCT. These measures were in healthy individuals with normal lung recoil. Subjects with compromised lungs, particularly in the case of emphysema, would be expected to show even greater lavage retention. Study protocols involving Q-MDCT and endobronchial lavage assessment should conduct imaging before lavage, or at a minimum of 24 hrs after lavage to avoid confounding effects of lavage on lung density metrics.

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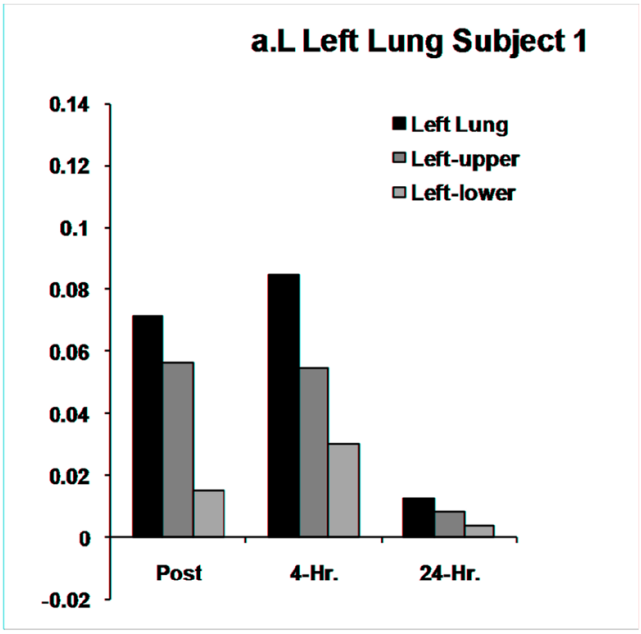

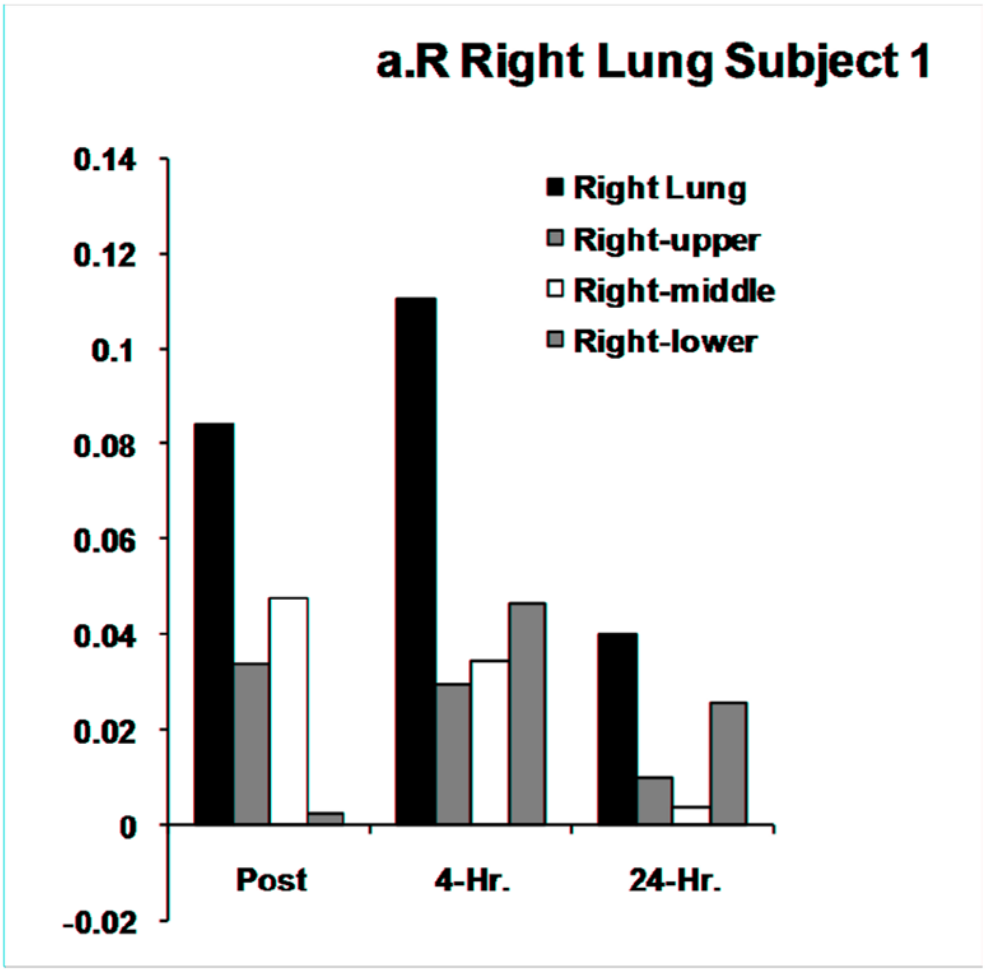

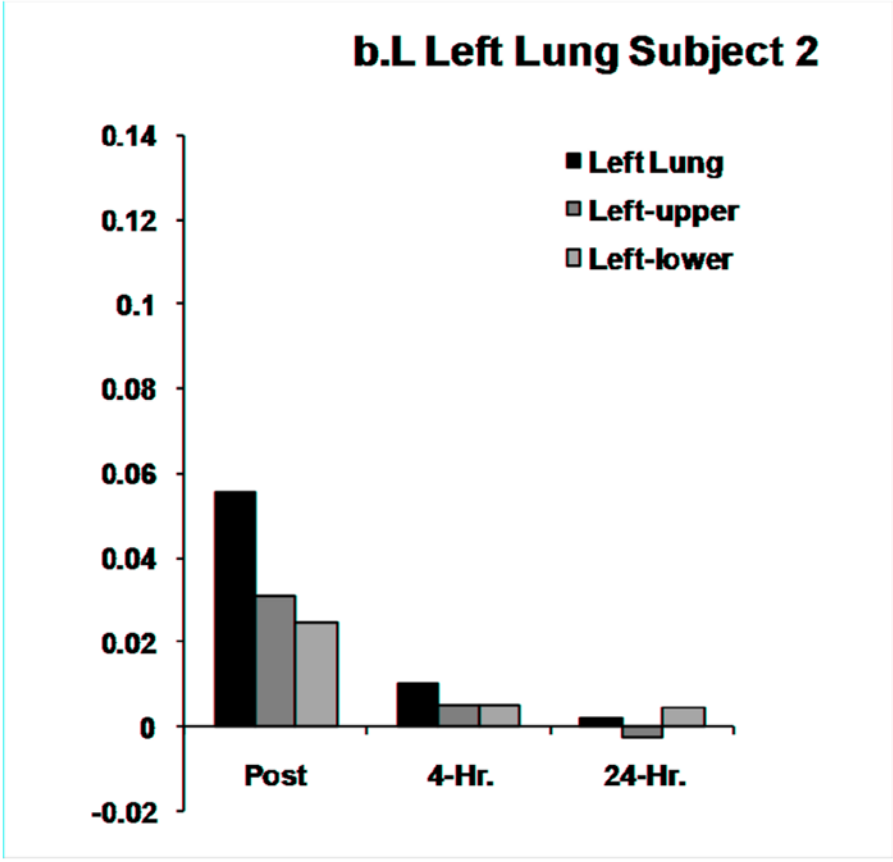

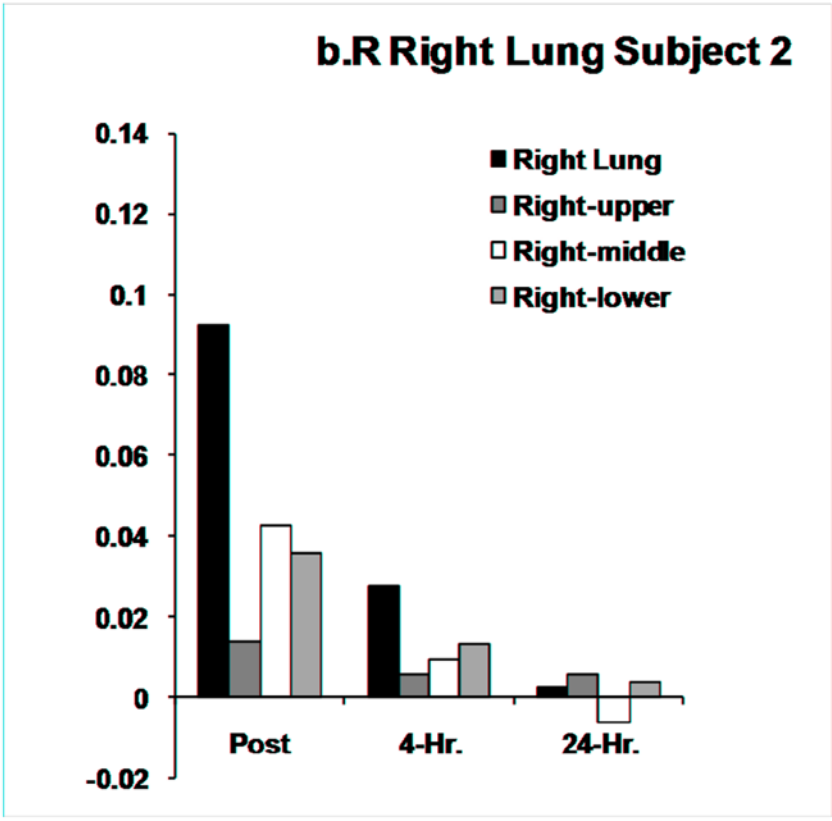

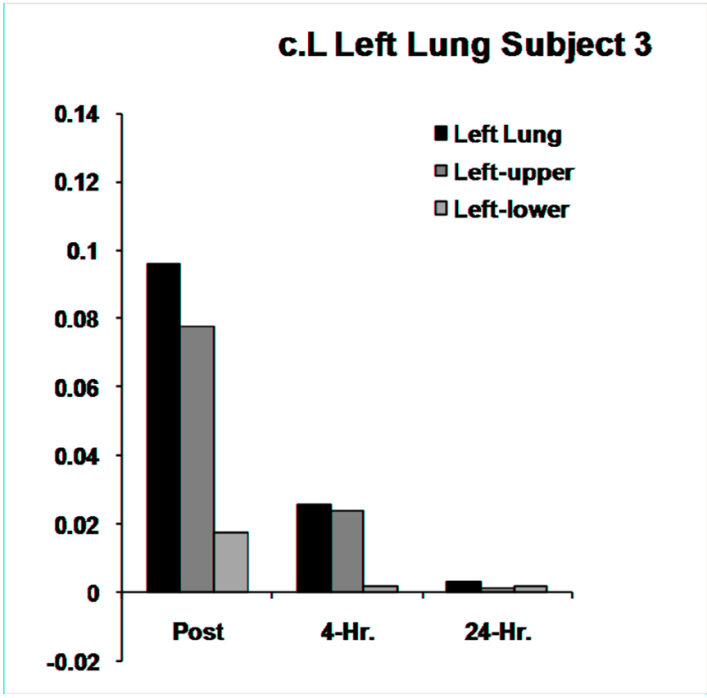

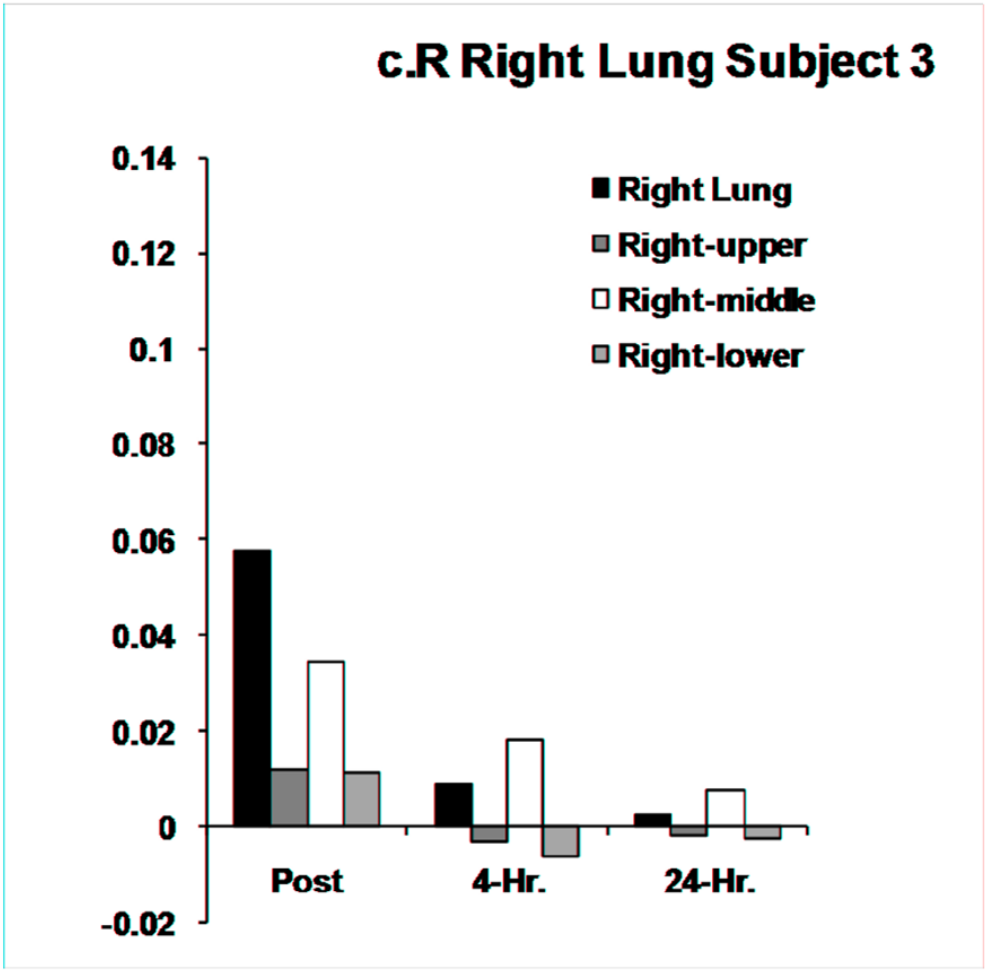

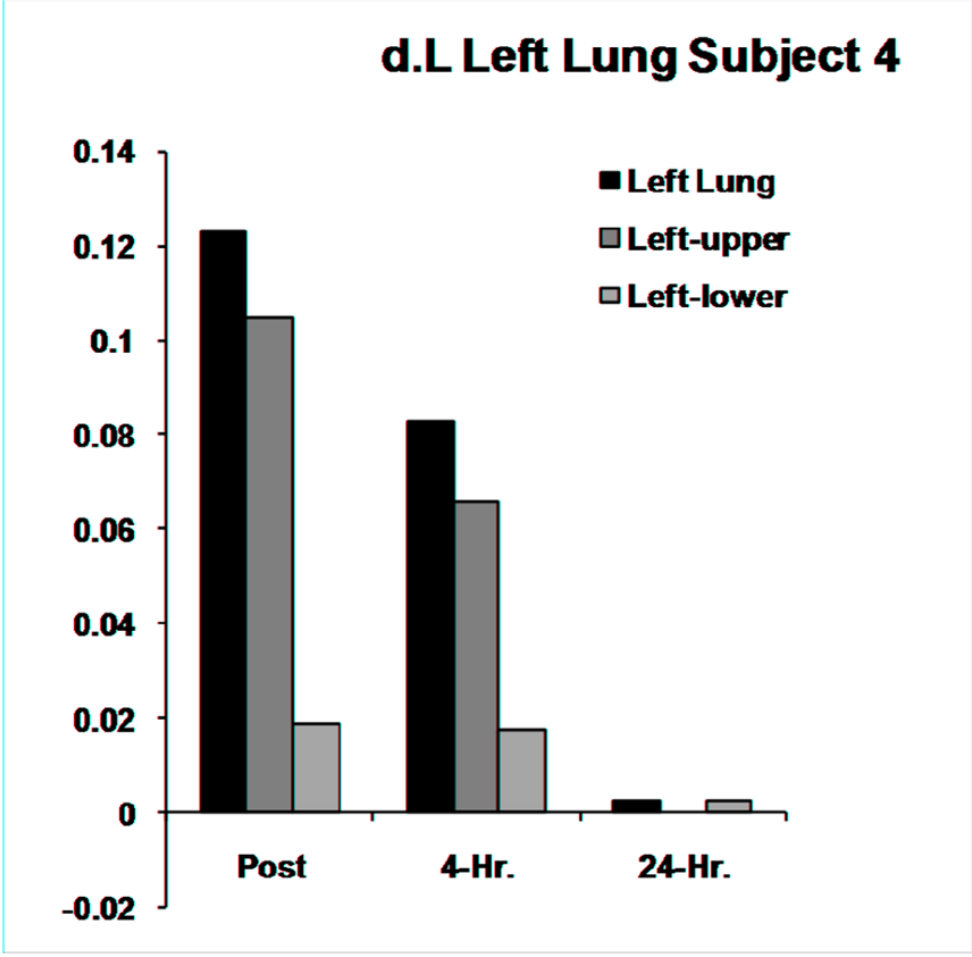

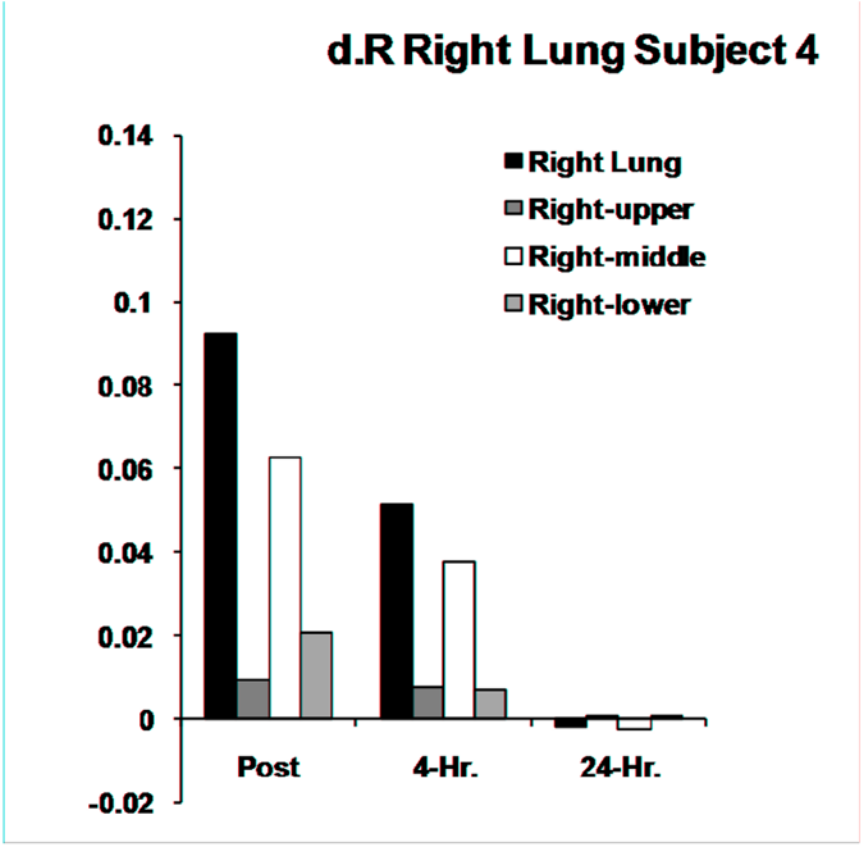

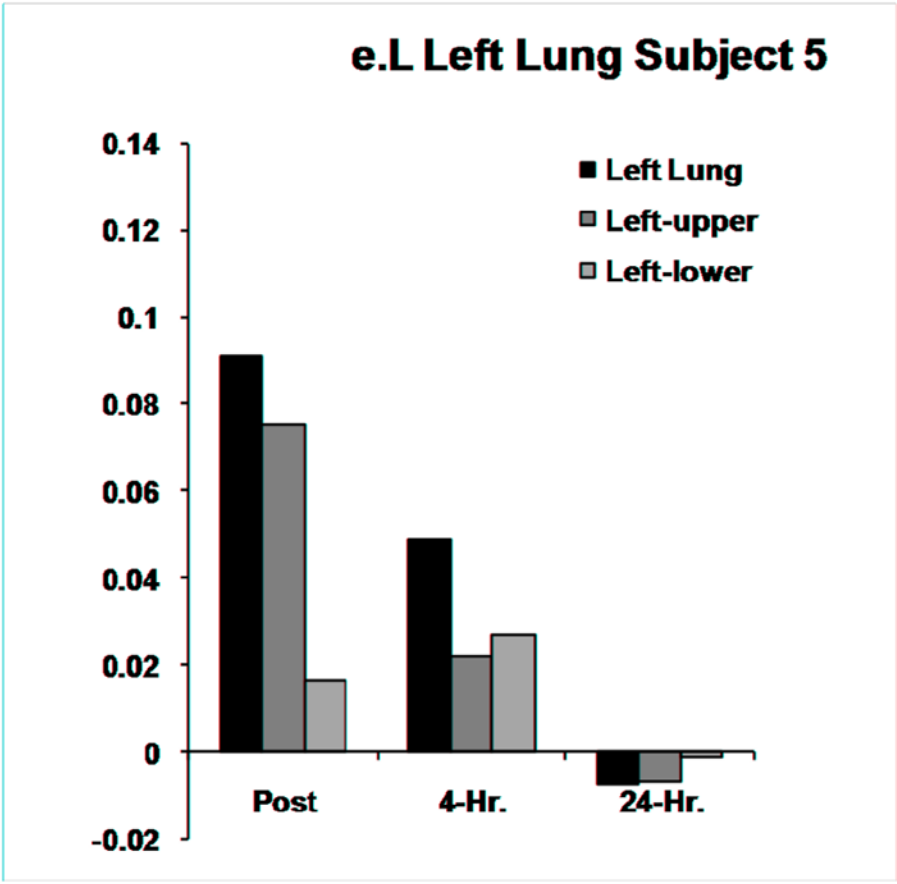

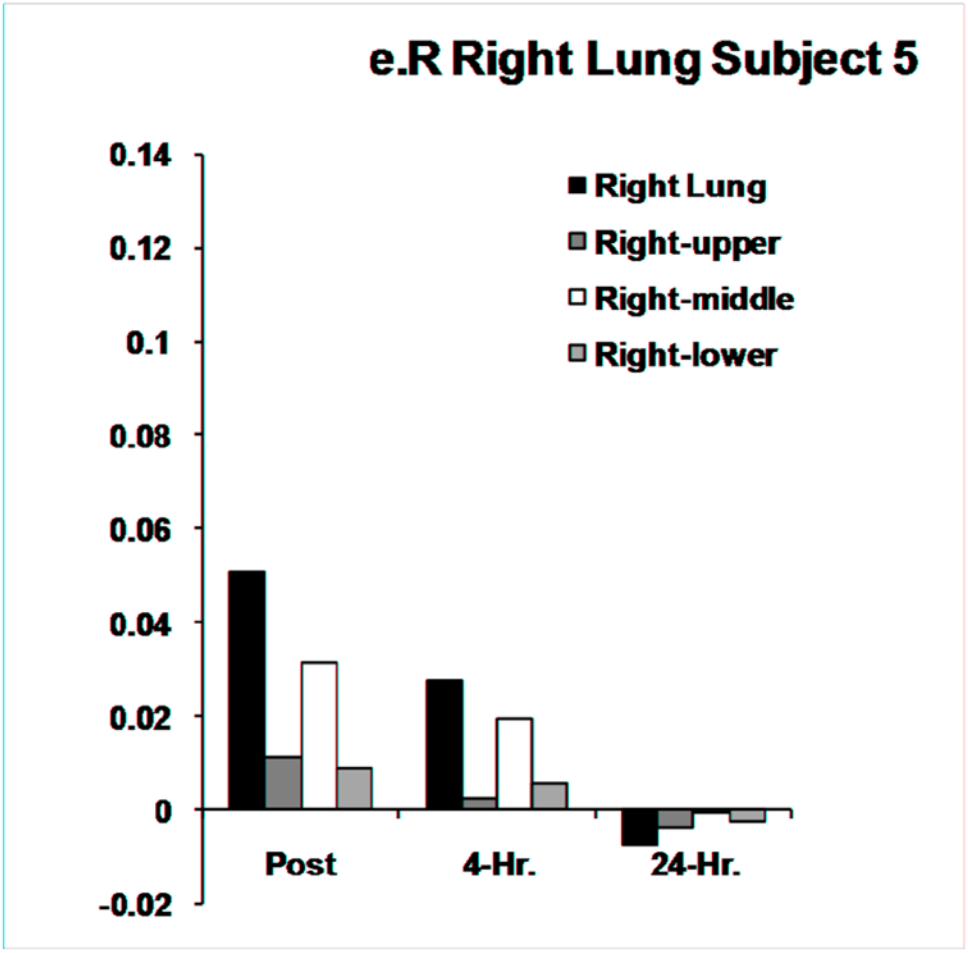

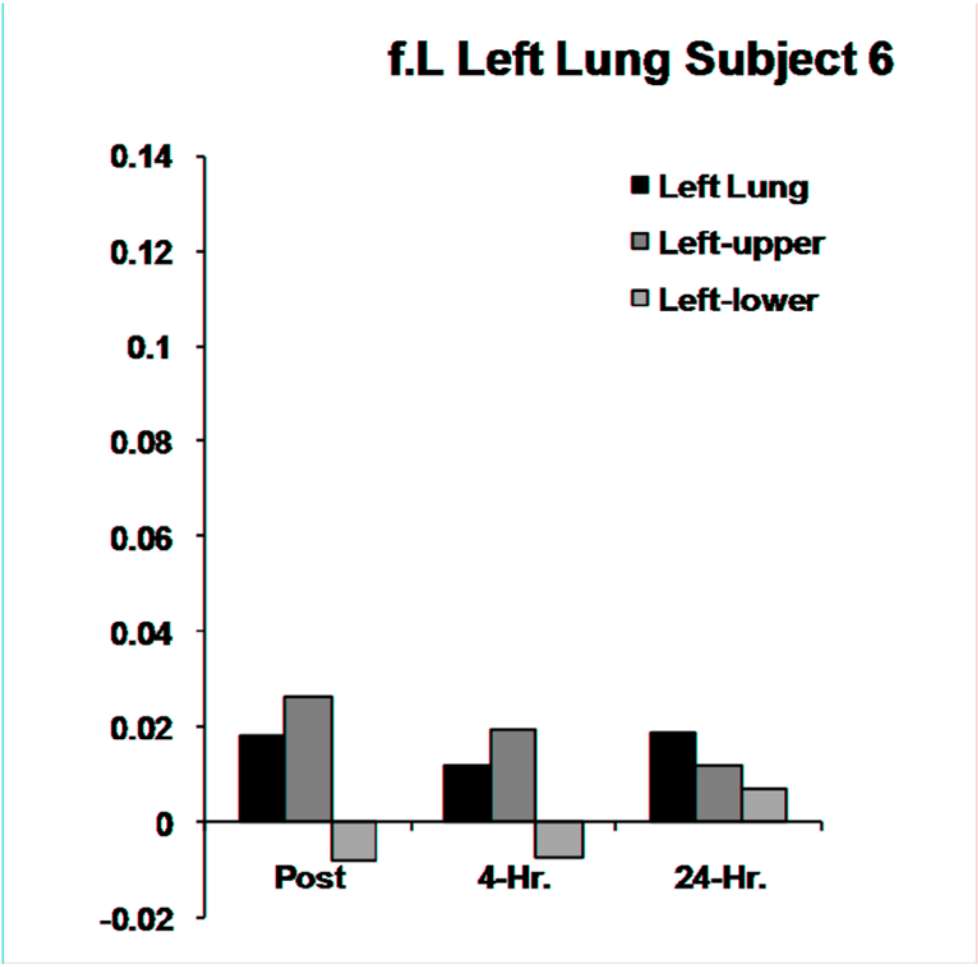

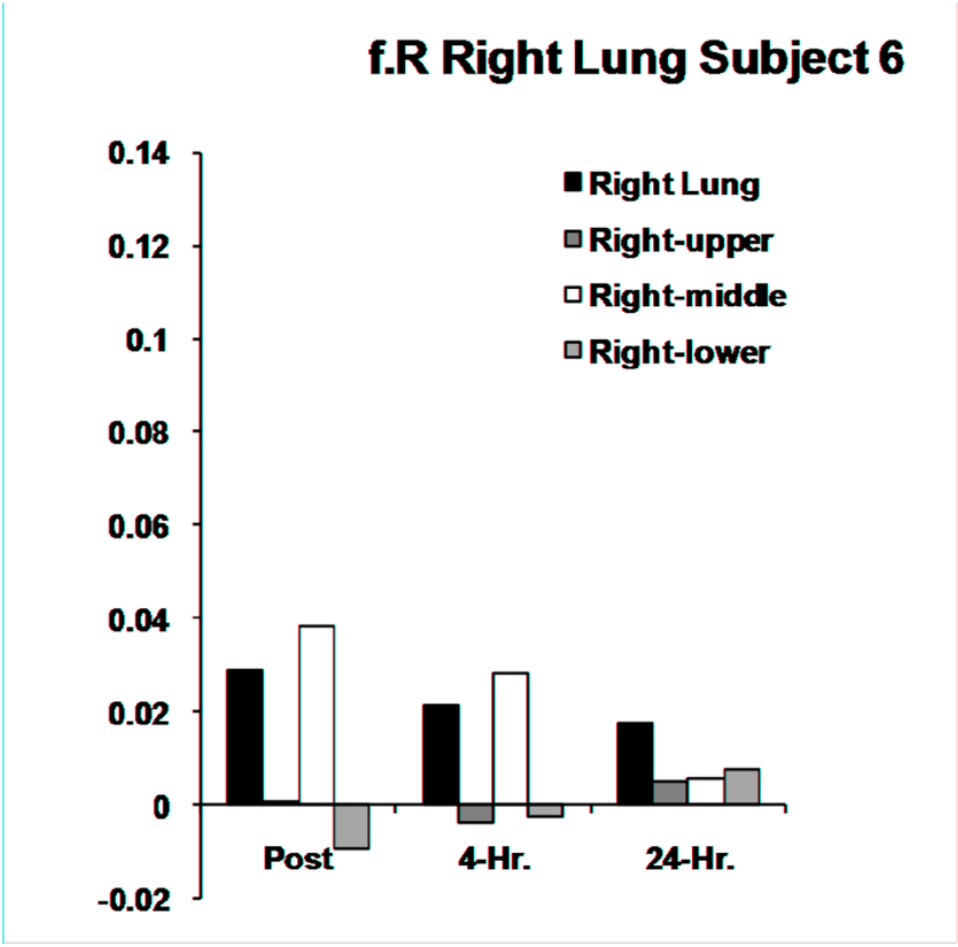

Figure 1.
Correlation of retained lavage fluid as reported by bronchoscopist and as assessed by volumetric densitometric CT on immediate post lavage scan. Top panel demonstrates the correlation for the whole lung while the lower panels depict the correlations for the left and right lungs separately. Note the strong correlation between the bronchoscopist's report and the CT-based quantitative findings for the whole lung plot (upper panel) and the poor correlation found at the level of the individual lungs (lower panels). We believe that this indicates that early after the BAL procedure, retained fluid redistributes not only between lobes but also between lungs.

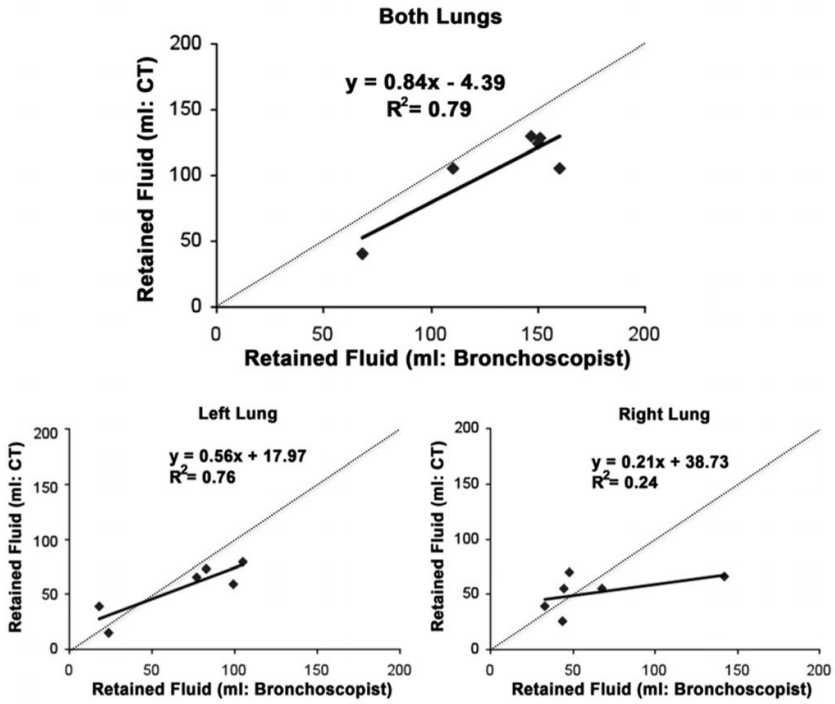

Figure 2.

Lower row: Average Non-air Volume among all subjects expressed as a percentage of baseline Non-air Volume. % Volumes significantly different from baseline ($p<.05$) can be found in table 3. Middle row: coronal sections shown across time with color-coding demonstrating the software-based division of the lung into individual lobar regions. **Upper row:** the same coronal images as shown in the middle row without the lobar color-coding. Arrows show the locations of maximal enhancement due to right middle lobe and lingular directed bronchoalveolar lavage. Note that to the eye, it is not clear that lavage fluid has distributed itself to all lung regions, as is evidence for the quantitative graphs in the bottom row.

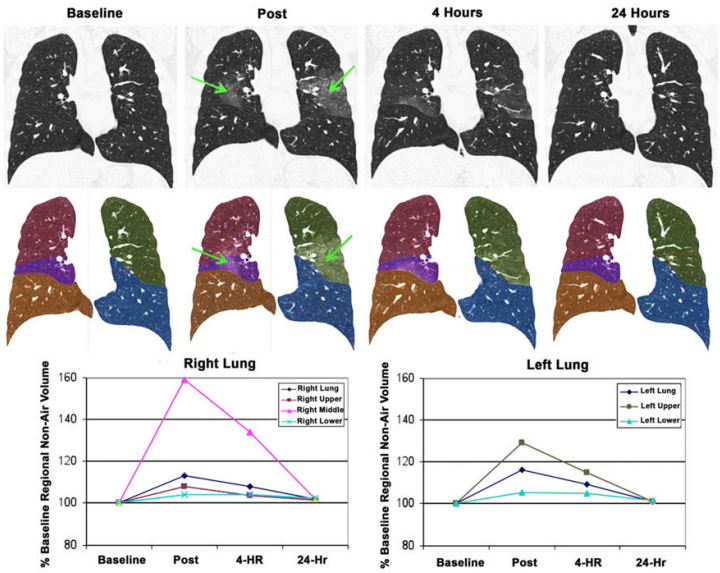

Figure 3.

Individual data for all subjects showing change in Non-air Volume relative to baseline scan. Values are calculated as [(Region Non-air) – (Region Baseline Non-air)]/(Lung Baseline Non-air). Considerable heterogeneity exists between subjects with respect to changes in Non-air Volume amongst lobes over time. With the exception of Subject 1(see discussion), Non-air Volume values return to near baseline at 24 hours.